

Statistical Methods for Improving Biosurveillance System Performance



**Associate Professor Ron Fricker
Naval Postgraduate School**

**Army Conference on Applied Statistics
October 17, 2007**

The New Status Quo?

"All the News That's Fit to Print"

The New York Times

National Edition
 South: Mostly cloudy and warm with scattered showers and storms, except partial sunshine near the Gulf coast and also in much of Georgia. Weather map and details are on Page C14.

VOL. CLII . . . No. 52,512 Copyright © 2003 The New York Times THURSDAY, JUNE 12, 2003 Printed in Georgia ONE DOLLAR

Smallpox Vaccinations Are Urged and Prairie Dogs Are Banned to Halt Monkeypox

By LAWRENCE K. ALTMAN
 The federal government recommended smallpox vaccinations yesterday for all those exposed to monkeypox, including pregnant women and children. It also banned the sale and distribution of prairie dogs in the nation and prohibited the importation of all rodents from Africa.

The Centers for Disease Control and Prevention also issued a list of signs and symptoms to determine which patients had monkeypox and to help in the agency's investigation of this potentially fatal viral disease. The actions seek to control the first outbreak of monkeypox in the Americas and to prevent importing it and other diseases endemic elsewhere in the world. Imported rodents are believed to have brought monkeypox to the United States from West and Central Africa, where it is endemic.

Yesterday, there were 54 cases of monkeypox under investigation in four states. Laboratory tests have confirmed monkeypox in 23 patients. Of the 54, Indiana reported 21 cases. Wisconsin reported 10 cases. Jersey reported 1 case.

Monkeypox is fatal in up to 10 percent of cases, much lower than the 30 percent figure for smallpox before it was eradicated worldwide in 1980. The government stopped routine smallpox vaccinations in 1979. The Bush administration began vaccinating health care workers this year in a program to protect against the infection after exposure.

The vaccine is given in two doses, one before and one after exposure. The vaccine is given to health care workers, laboratory workers, and others who may be exposed to the disease from a bioterrorist attack.

Of 54 suspected cases, four states and countless questions.

Dogs and importing rodents from Africa took effect immediately and will remain in effect until health officials can determine the safety of such importations.

Senators James M. Jeffords, independent of Vermont, and John Ensign, Republican of Nevada, yesterday called for an Environment and Public Works Committee hearing on regulations on importing exotic pets.

ing sick animals after they had been checked by a veterinarian. Federal health workers are tracking shipments of potentially infected animals to help prevent the spread of monkeypox and to reduce the chances of the disease gaining a permanent foothold. The disease centers included these signs and symptoms for monkeypox: a rash consisting of raised bumps.

Mystery outbreak's global reach grows

By M.A.J. McKENNA
 cases of the illness was taken plane in Frankfurt his pregnant wife er after he develo- tions. On Monday, said the wife was

Anthrax Found in NBC News Aide

Suspicious Letter Is Tested at Times — Wide Anxiety

By DAVID BARSTOW
 An assistant to the NBC anchor Tom Brokaw has tested positive for anthrax infection more than two weeks after she opened a threatening letter addressed to Mr. Brokaw that contained a white powder, officials said yesterday.

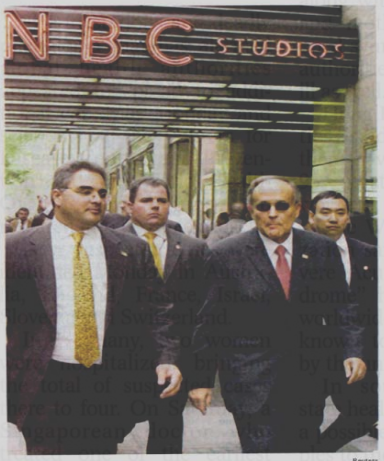
Even as law enforcement officials were cordoning off Rockefeller Center, the newsroom at The New York Times was evacuated when a reporter opened an envelope that also contained a white powder.

The substance was still being tested last night, as investigators explored potential links between the two incidents. Both letters were mailed from St. Petersburg, Fla., and had similar handwriting, according to law enforcement officials.

The reports of possible bioterrorism caused widespread anxiety in New York and across the country. People depleted supplies of antibiotics at drugstores and besieged their doctors. Offices were evacuated after a spate of threats, and companies made emergency adjustments to the way they received mail. (Page B9.)

The NBC case marked the second time an American has been stricken with a form of anthrax since the Sept. 11 terror attacks.

In the other case, a man died after he contracted an inhaled form of the disease at a newspaper office in Boca Raton, Fla. Two other people at the office were exposed to anthrax.



Mayor Rudolph W. Giuliani at a news conference yesterday at NBC, where he tried to calm new fears that were raised by an anthrax case.



Travelers wear masks to ward off Asia's mystery illness at Hong Kong's Chek Lap Kok airport on Monday.

Internationally, tensions eased slightly after the government of China said it will provide information to the global health agency about a pneumonia outbreak four months ago. A12

Please see ILLNESS, A12

WEST NILE CASES RAISING QUESTIONS OVER TRANSPLANTS

WEST NILE CASES RAISING QUESTIONS OVER TRANSPLANTS

Determine if transfusion missions

ALTMAN

two weeks to West Nile vi- through organ transfusions to a ant recipients has been diag- federal health

INSIDE

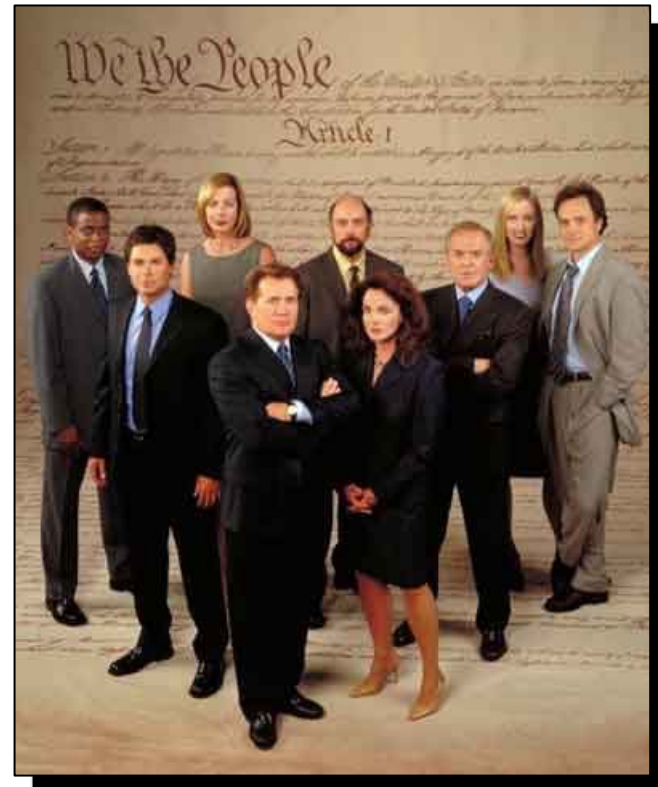
Chinese government asks the World Health Organization to help identify the cause of a pneumonia outbreak four months ago. A12

Bioterrorism Threat Recognized Pre-9/11 – Even in Popular Culture...

“That’s how it’s gonna be, a little test tube with a-a rubber cap that’s deteriorating... A guy steps out of Times Square Station. Pshht... Smashes it on the sidewalk... There is a world war right there.”

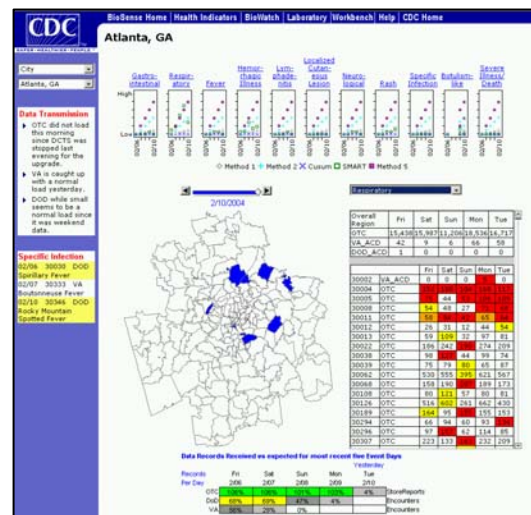
“Josh”

West Wing, 1999



Syndromic Surveillance as a Form of Biosurveillance

- “...surveillance using health-related data that precede diagnosis and signal a sufficient probability of a case or an outbreak to warrant further public health response.” [1]
- On-going discussion in public health community about use of syndromic surveillance for “early event detection” vs. “situational awareness”



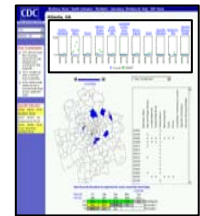
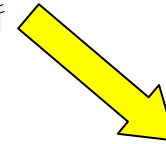
[1] CDC (www.cdc.gov/eпо/dphsi/syndromic.htm, accessed 5/29/07)

Idea of Syndromic Surveillance: Leverage Secondary Health Data

- Ideal is automatic or near real-time data analysis
- Use data, methods to allow for identification of subtle trends not visible to individual MD's
- Provide indicators to trigger detection, investigation, quantification, localization, and outbreak management



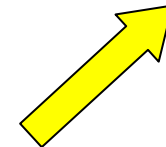
**Clinical
Data and
Lab Results**



**Syndromic
Surveillance
System**



**Other Early
Detection Data**



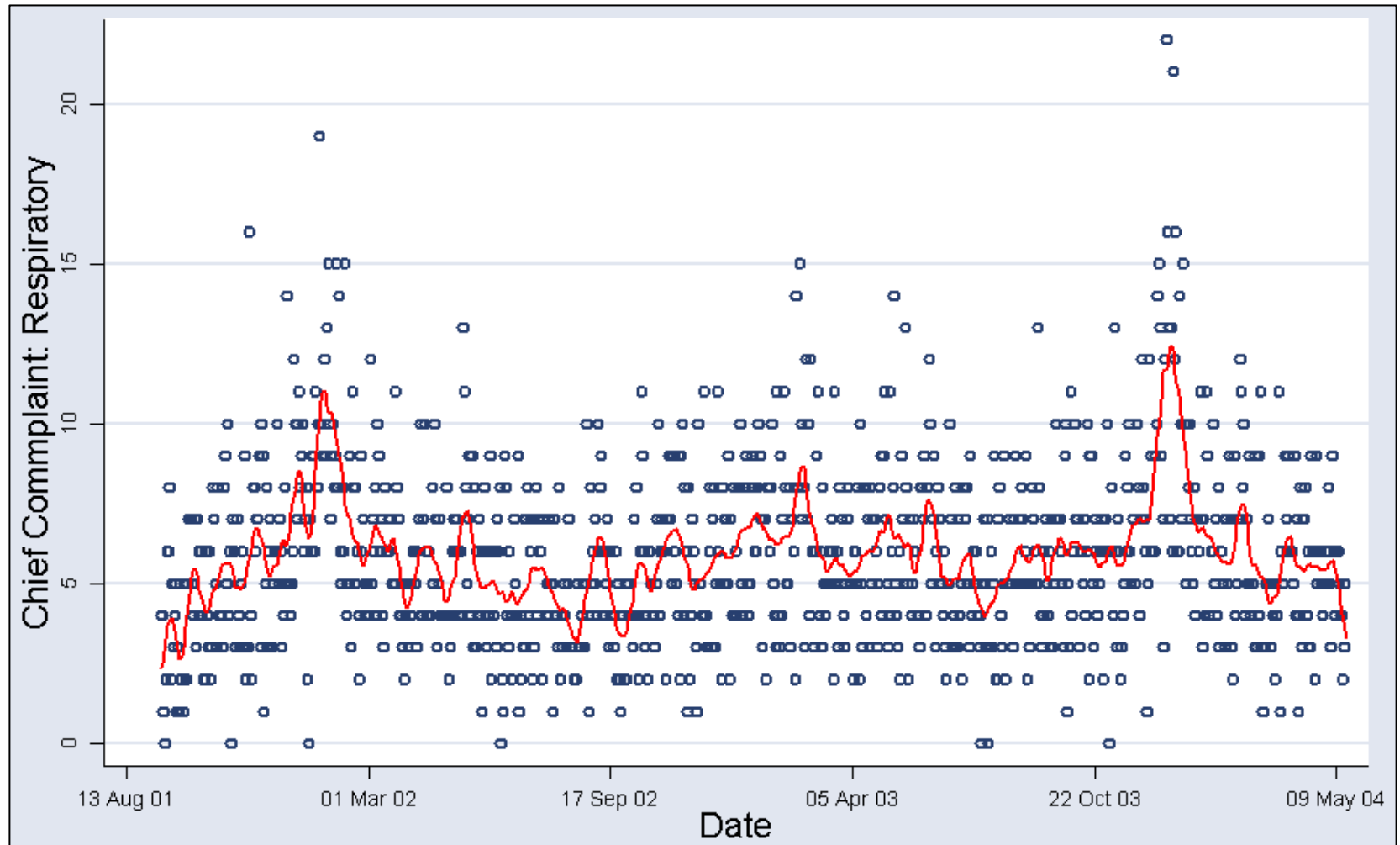
Statistical Process Control (SPC) for Syndromic Surveillance

- In manufacturing setting, SPC used to monitor production and test for a change level of quality
 - Sequential hypothesis test for distributional parameter(s) of quality characteristic (often the mean)
- In syndromic surveillance, goal is to monitor whether a pathogen has been released
 - Test whether distribution of leading indicators has shifted in some meaningful (i.e., worrisome) way
 - Focus needs to be on nonspecific—but relevant—symptoms
 - If symptoms are obvious and specific, then observation by clinician is likely sufficient

Challenges in Developing Statistical Methods for Syndromic Surveillance

- Nonstationary data
 - No control over “in-control” distribution
- Systematic effects
 - Seasonal, day-of-the-week and other effects in data
- Transient “out-of-control” conditions
 - Outbreaks/attacks begin, peak, and subside
- Vague alternative hypotheses
 - Detect only bioterrorism or natural diseases too?
 - Which diseases and/or outbreak manifestations?

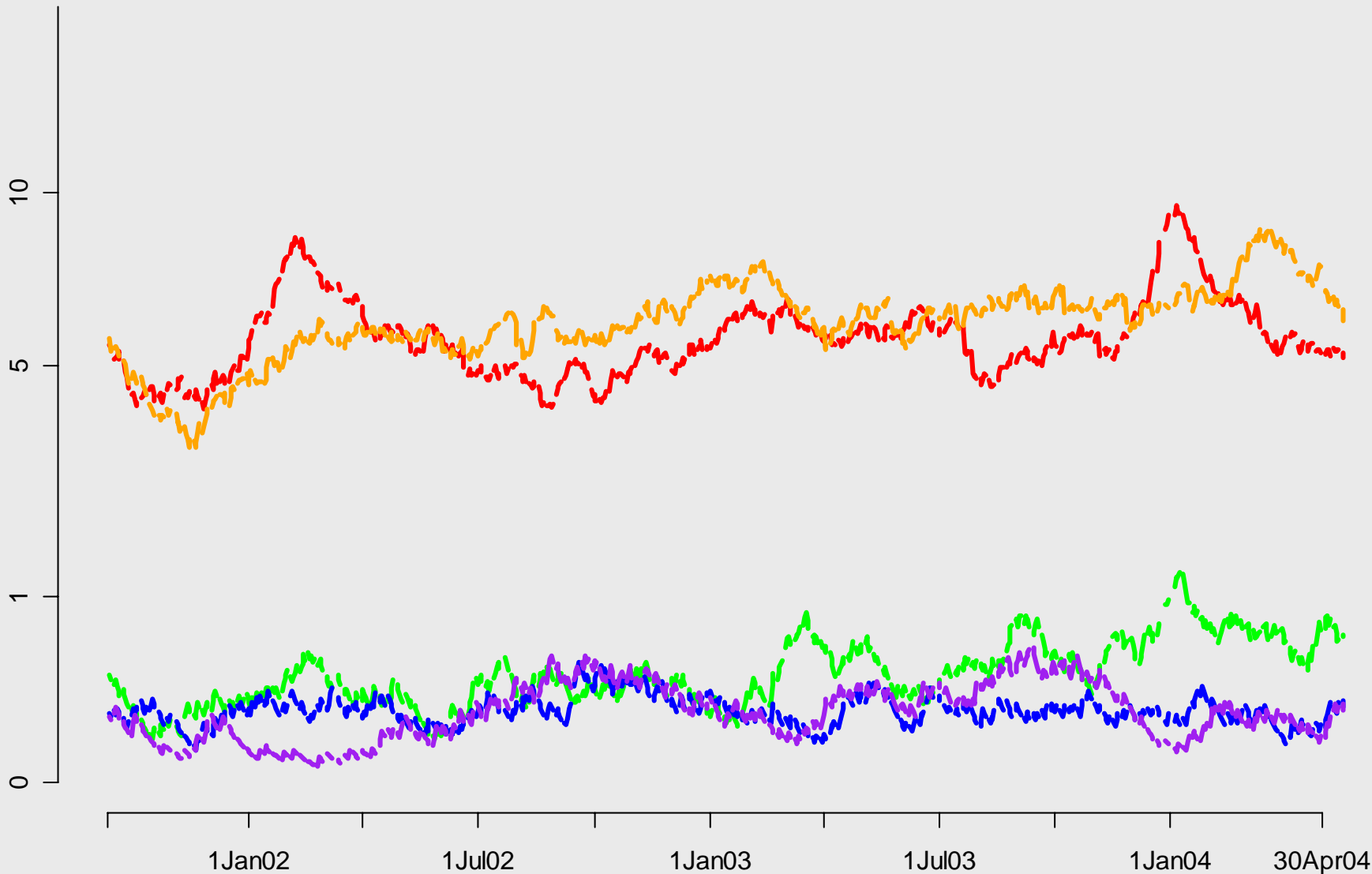
Challenges in Developing Statistical Methods for Syndromic Surveillance



Respiratory Data From “Hospital C”

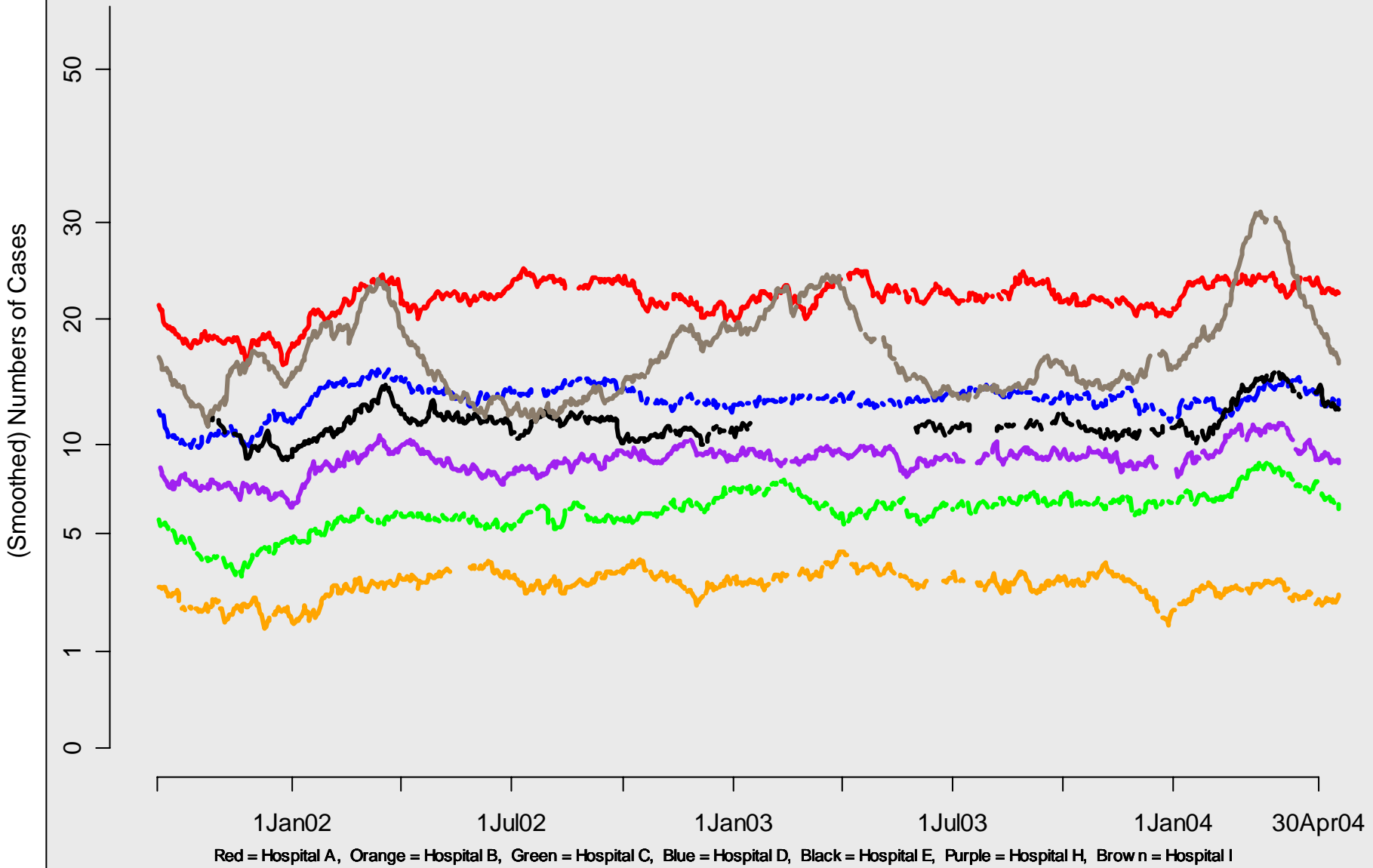
Hospital C: Different Syndromes over Time

(Smoothed) Numbers of Cases



Red = Resp, Orange = Gastro, Green = Unspecified Infection, Blue = Neuro, Purple = Rash

Gastro Cases at Different Hospitals over Time



Improving Statistical Methods for Syndromic Surveillance

- Focus areas:
 - Improve on / adapt existing temporal methods
 - Those currently in use in biosurveillance systems
 - Statistical process control methods
 - Create and assess methods for optimizing biosurveillance systems
 - Develop / improve spatio-temporal methods

Focus Area #1: Improving on Existing Temporal Methods ^[1]

- Early Aberration Reporting System (EARS)



- Designed to be a “drop-in” surveillance system
 - Often little historical information available
- Available on the web^[2], so increasingly being used as standard health surveillance system

[1] Based on joint work with B. Hegler and D. Dunfee

[2] www.bt.cdc.gov/surveillance/ears

EARS' Methods: C1, C2, and C3

$$C_1(t) = \frac{Y(t) - \bar{Y}_1(t)}{s_1(t)}$$

- Sample statistics calculated from previous 7 days' data
- Stop when statistic > 3

$$C_2(t) = \frac{Y(t) - \bar{Y}_3(t)}{s_3(t)}$$

- Sample statistics calculated from 7 days' of data prior to 2 day lag
- Stop when statistic > 3

$$C_3(t) = \sum_{i=t}^{t-2} \max[0, C_2(i) - 1]$$

- Stop when statistic > 2

Alternative: CUSUM on Residuals from “Adaptive Regression”

- Adaptive regression: regress a sliding baseline of observations on time relative to current observation
 - I.e. regress $Y(t-1), \dots, Y(t-n)$ on $n, \dots, 1$
- Calculate standardized residuals from one day ahead forecast, $X(t) = R(t) / \sigma_Y$, where

$$R(t) = Y(t) - \left[\hat{\beta}_0 + \hat{\beta}_1 \times (n+1) + \hat{\beta}_j \right]$$

- CUSUM:

$$S(t) = \max \left[0, S(t-1) + X(t) - k \right]$$

with

$$k = \frac{1}{2} \sqrt{\frac{(n+2)(n+1)}{n(n-1)}}$$

Comparison Methodology

- Generate synthetic data:

$$Y(t) = \max \left(0, \left[c + s(t) + d(t) + Z(t) + o(t) \right] \right)$$

- Scenarios:

	None	Small	Large
A	0	20	80
σ	n/a	10	30

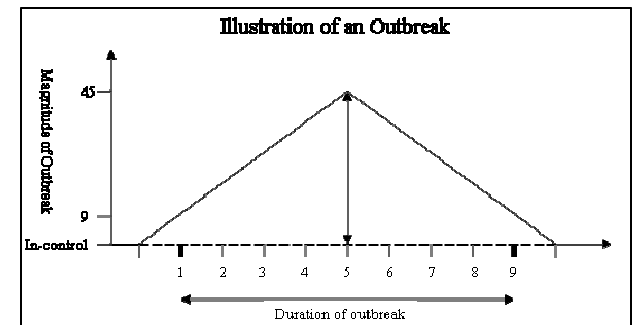
Large count: c=90

	None	Small	Large
A	0	2	6
μ, σ	n/a	1.0, 0.5	1.0, 0.7

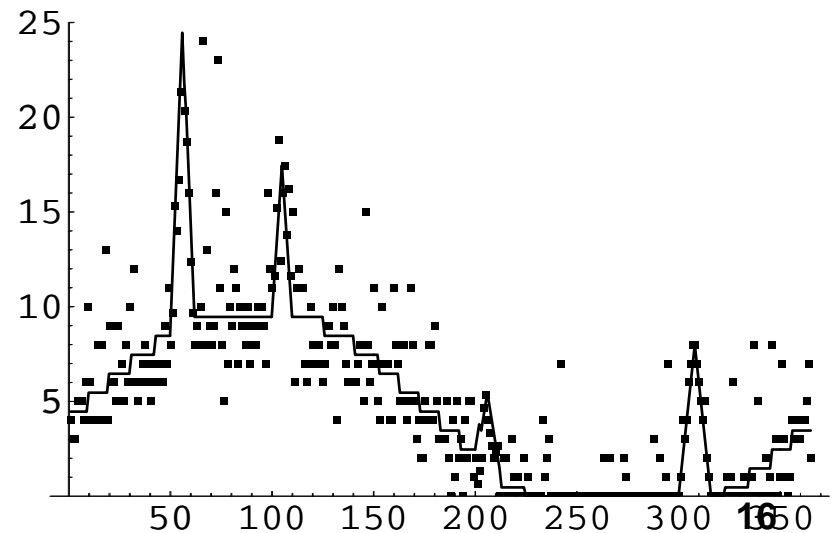
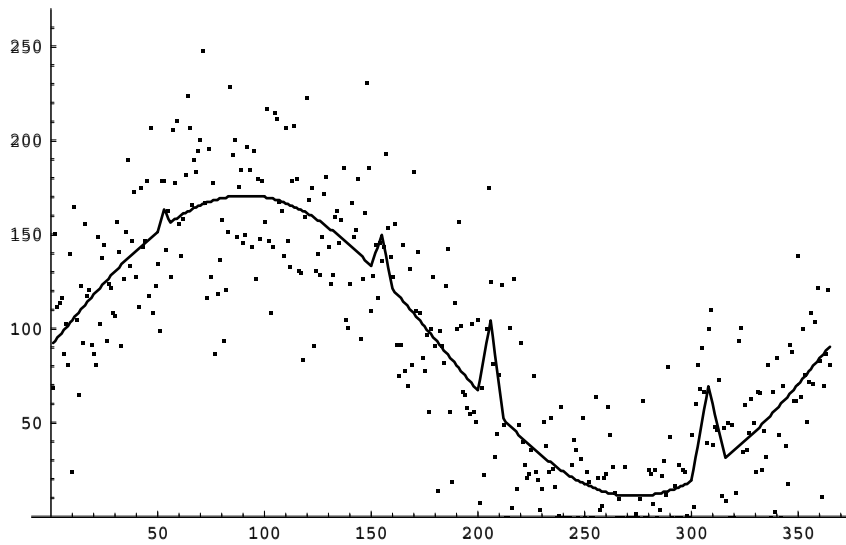
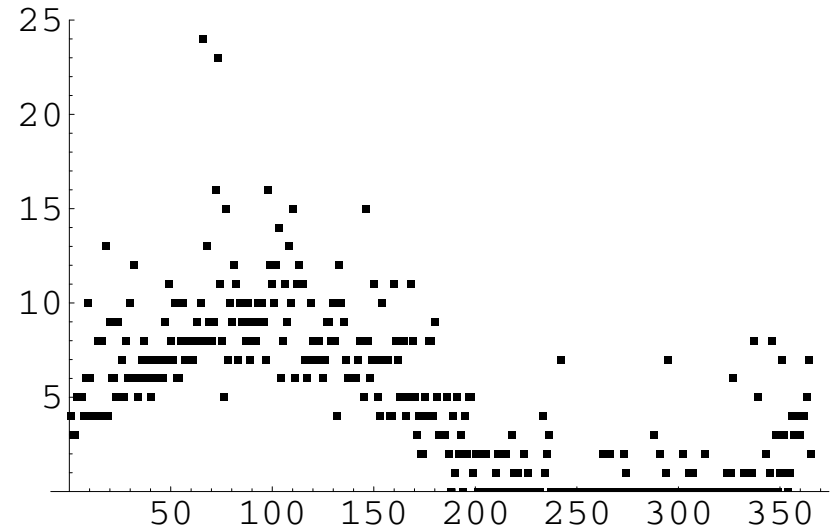
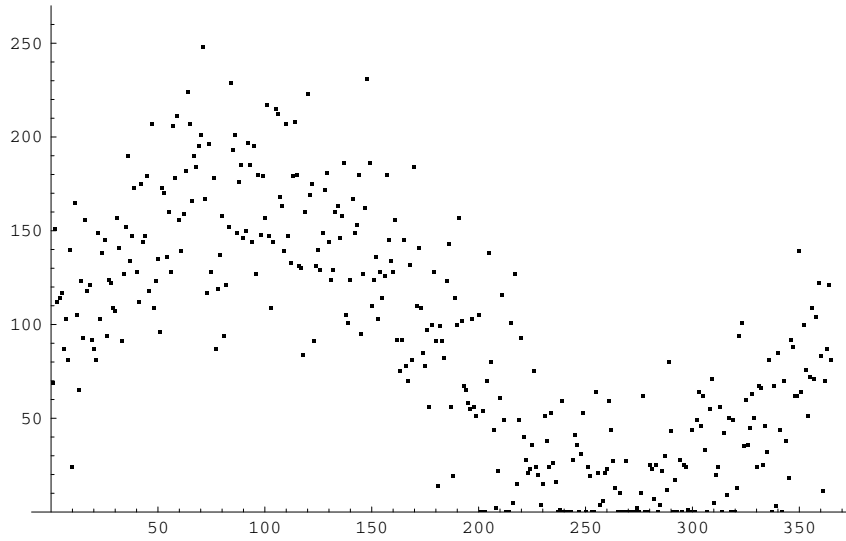
Small count: c=0

- Outbreaks

- Linear increase & decrease
- Characterized by duration and magnitude



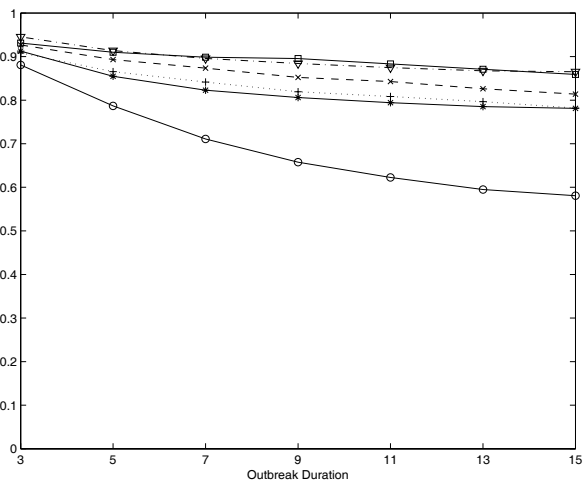
Synthetic Data: Outbreaks?



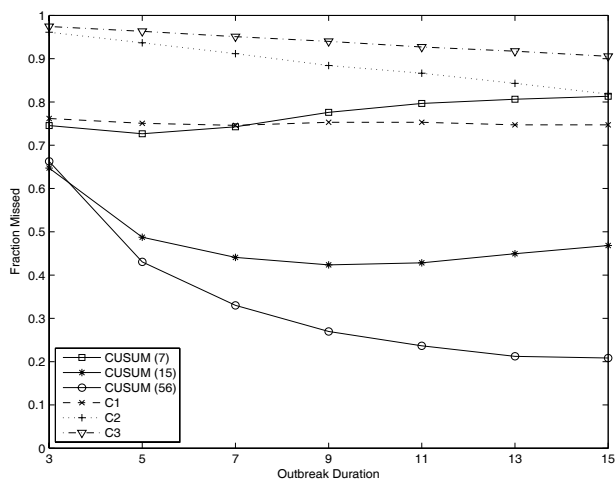
Some Large Count Results

Small magnitude

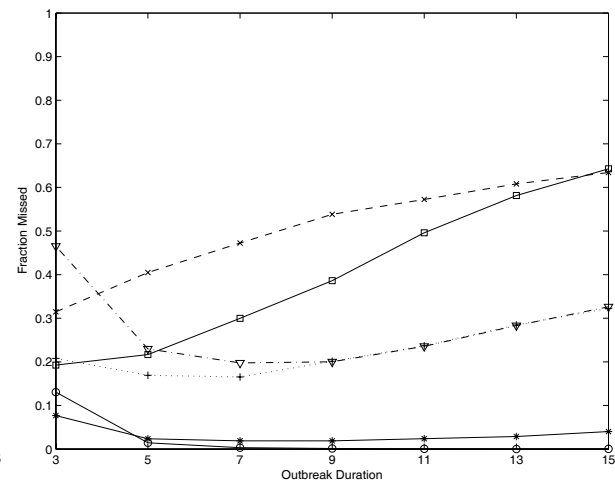
Fraction Missed



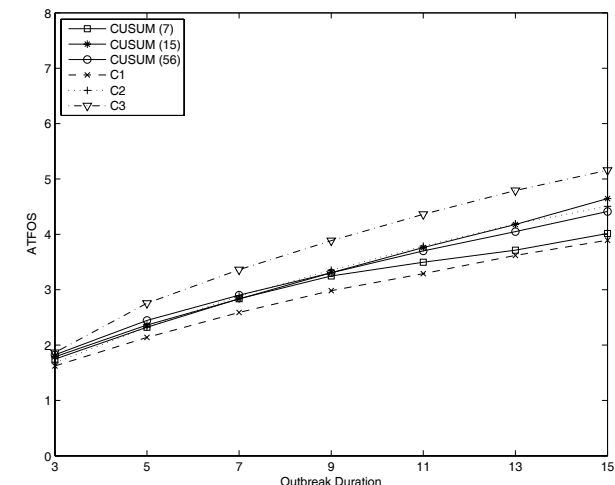
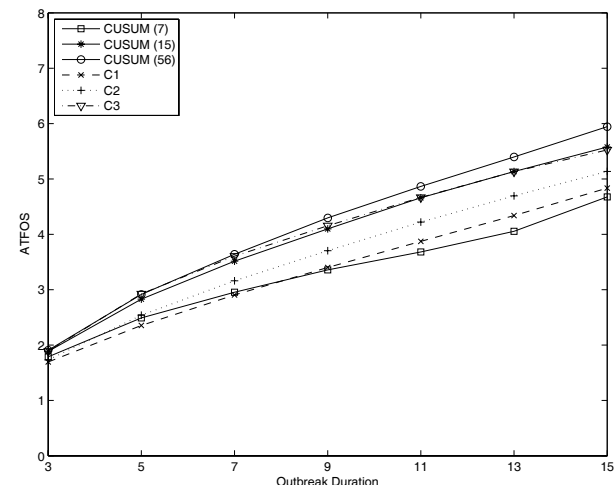
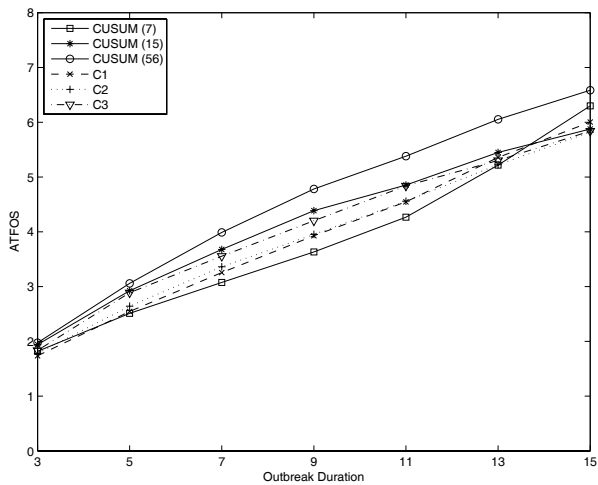
Medium magnitude



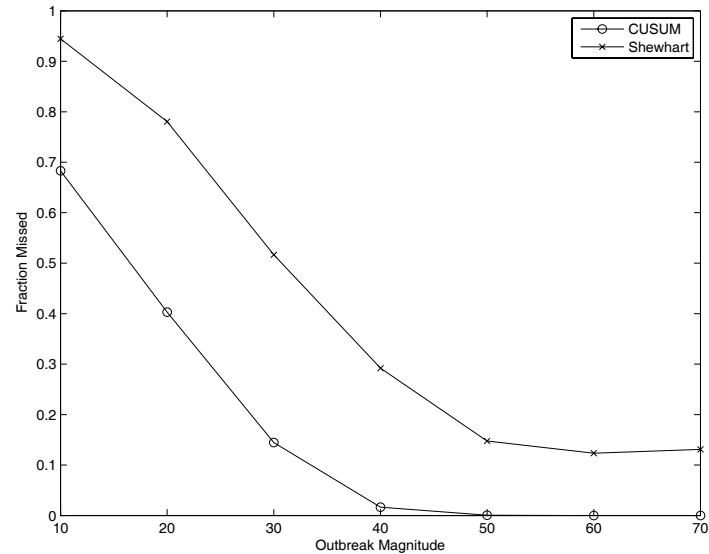
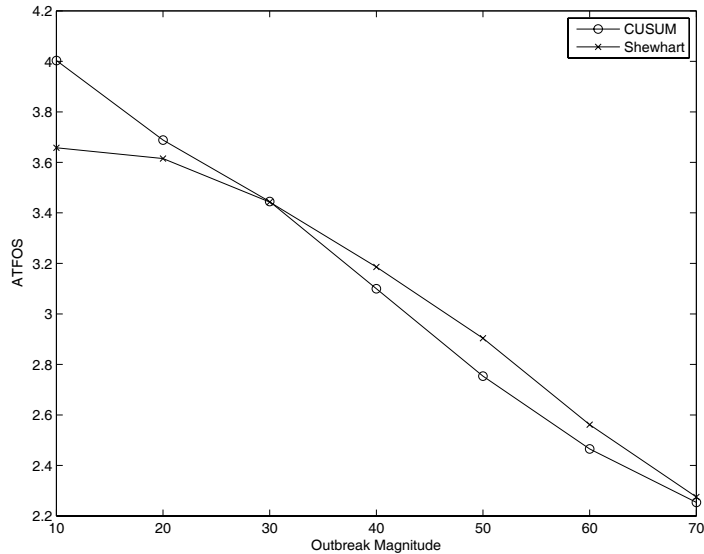
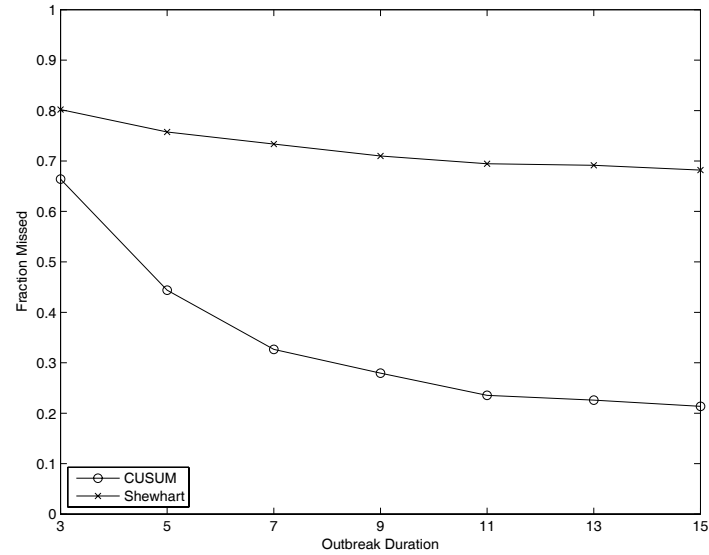
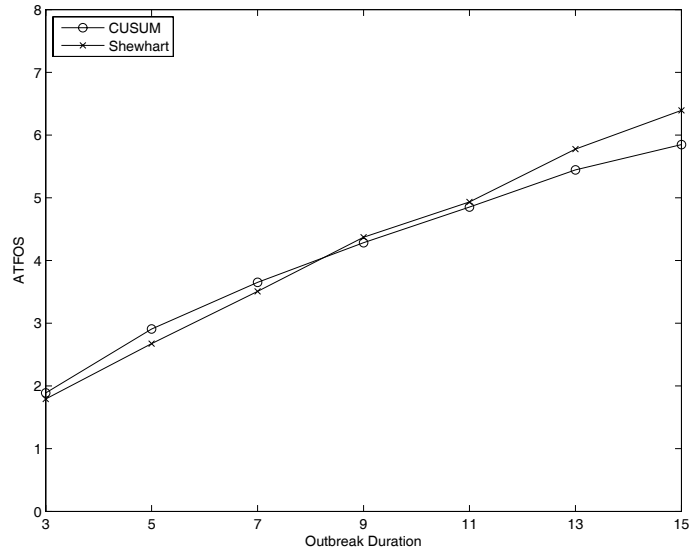
Large magnitude



Avg Time to Signal



Shewhart Methods Not Suited for this Problem?



Observations

- CUSUMs based on adaptive regression with longer baselines performed best
- CUSUMs outperformed EARS' methods
 - Seemingly due to Shewhart design *and* additional data used in adaptive regression
- Suggests “drop in” strategy of starting with CUSUM with 7-day baseline
 - As time progresses, increase baseline until long enough to allow it to slide

Focus Area #2:

Optimizing Biosurveillance Systems [1]

- False alarms a serious problem

“...most health monitors, who are the users of such systems, learned to ignore alarms triggered by their system. This is due to the excessive false alarm rate that is typical of most systems - there is nearly an alarm every day!” [2]

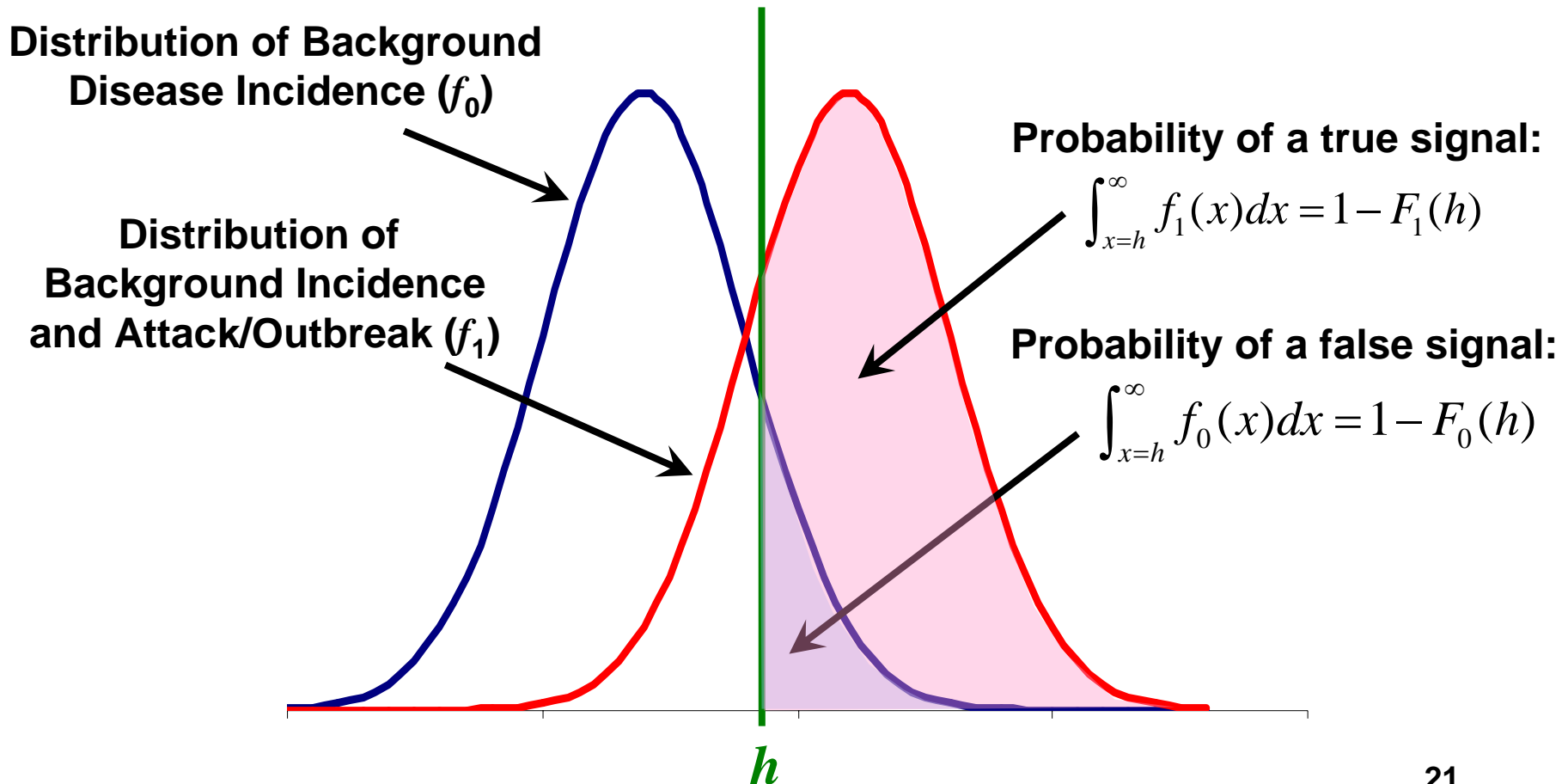
- Issue: How to optimize the system?
 - I.e., How to choose thresholds to maximize the probability of detecting an attack within a manageable false alarm rate

[1] Based on joint work with D. Banschbach

[2] <https://wiki.cirg.washington.edu/pub/bin/view/Isds/SurveillanceSystemsInPractice>

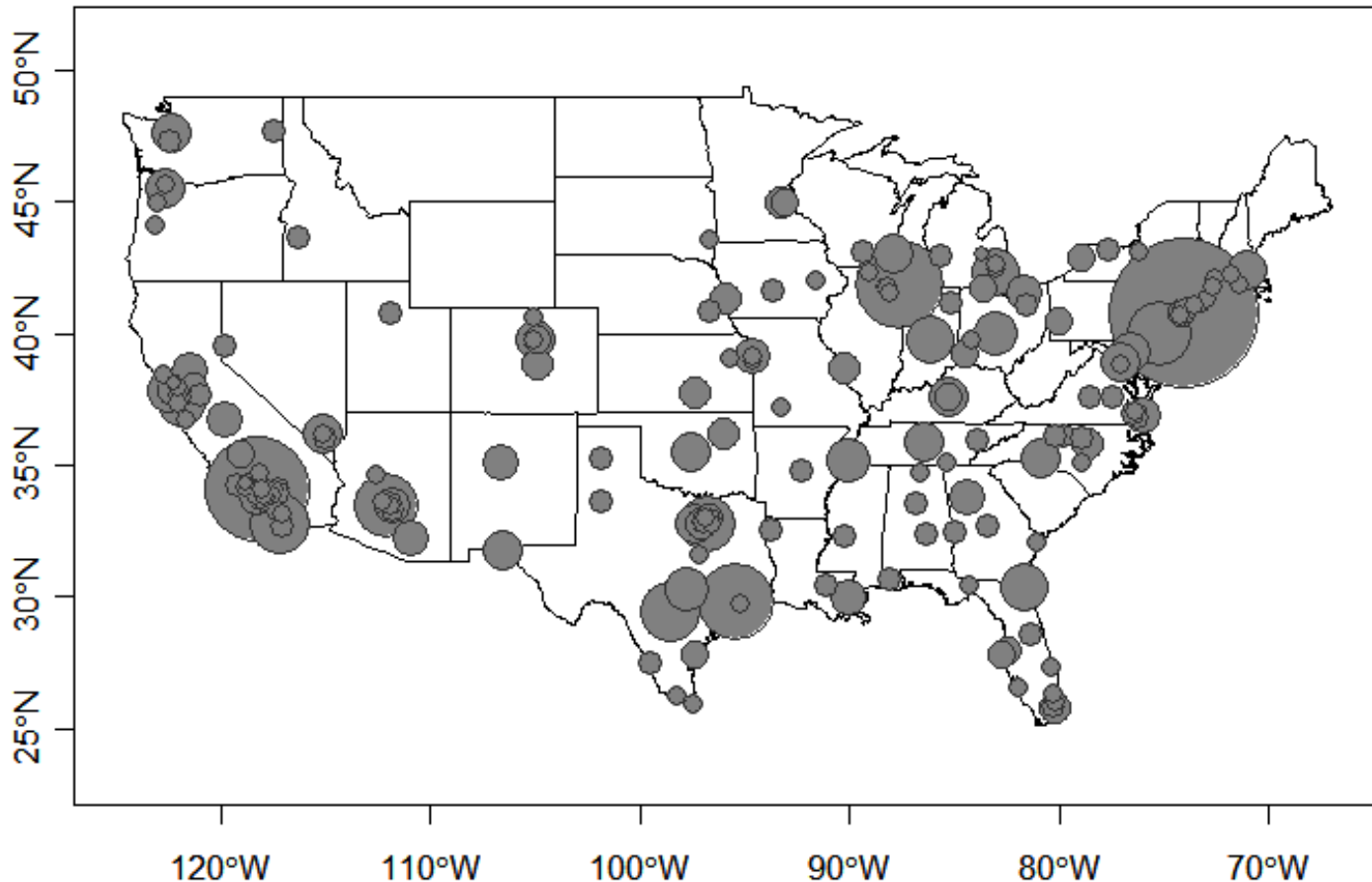
Threshold Detection Methodology

- Signal if observation exceeds threshold h



Consider (Hypothetical) System to Monitor 200 Largest Cities in US

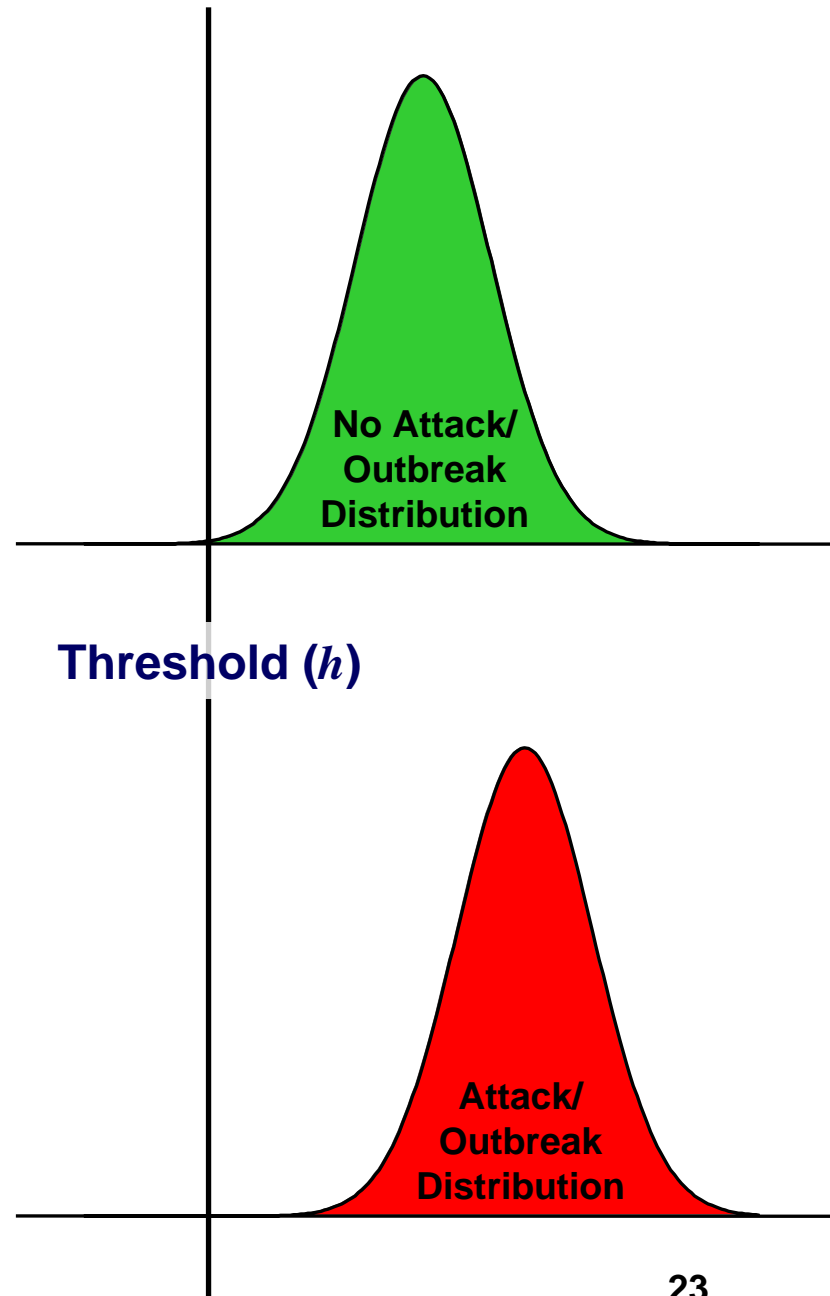
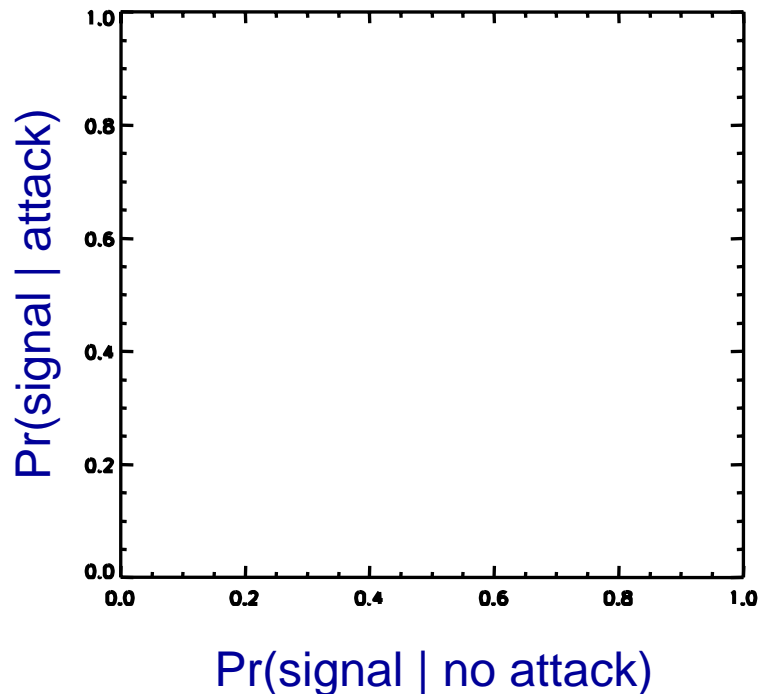
- Assume probability of attack is proportional to the population in a city: $p_i = m_i / \sum_i m_i$



It's All About Choosing Thresholds

- For each city, choice of h is compromise between probability of true and false signals

ROC Curve



Mathematical Formulation of the Problem

- It's simple to write out:

$$\Pr(\text{detection}) = \sum_i \Pr(\text{signal}|\text{attack}) \Pr(\text{attack})$$

$$E(\# \text{ false signals}) = \sum_i \Pr(\text{signal}|\text{no attack})$$

- Express it as an optimization problem:

$$\max_{\vec{h}} \sum_i [1 - F_1(h_i)] p_i$$

Choose thresholds to maximize the probability of detecting an attack

$$\text{s.t.} \quad \sum_i [1 - F_0(h_i)] \leq K$$

Subject to a constraint on the expected number of false alarms

Visualizing an Objective Function and Feasible Region

- Consider a simple two-sensor problem:
 - $F_0 = N(0,1)$ & $F_1 = N(1,1)$
 - Equal probability of attack at either sensor
 - Constraint: $\alpha_1 + \alpha_2 \leq 0.2$
- In general, global optimal solution exists if, over the feasible region:
 - F_0 and F_1 concave
 - F_1 strictly increasing

Figure 1 Plot of an objective function for $n=2$ with $F_0 = N(0,1)$, $F_1 = N(1,1)$ and $\mathbf{p} = \{1/2, 1/2\}$.

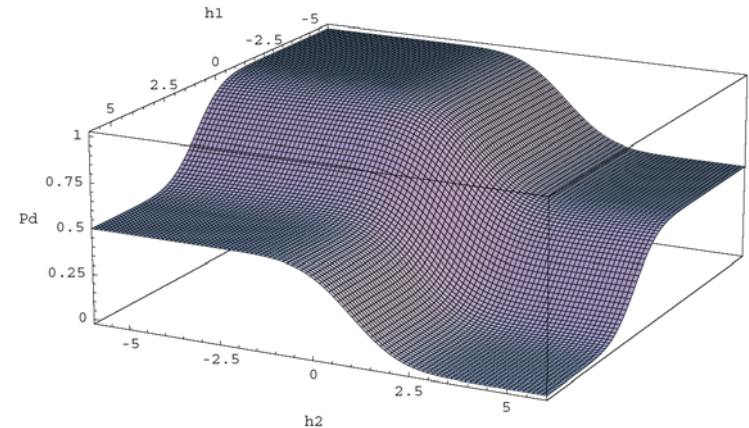
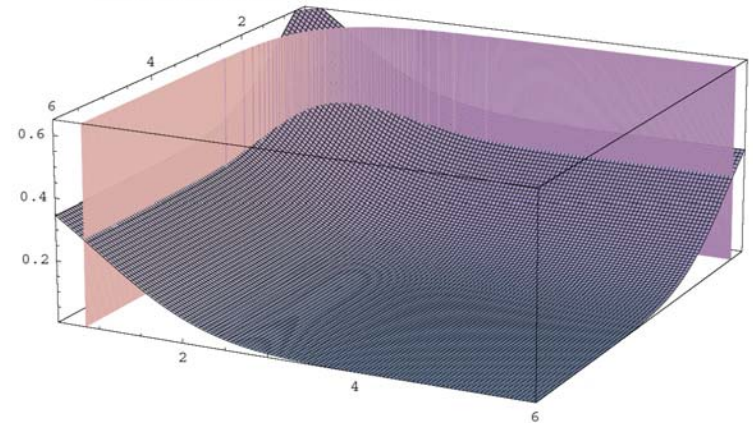
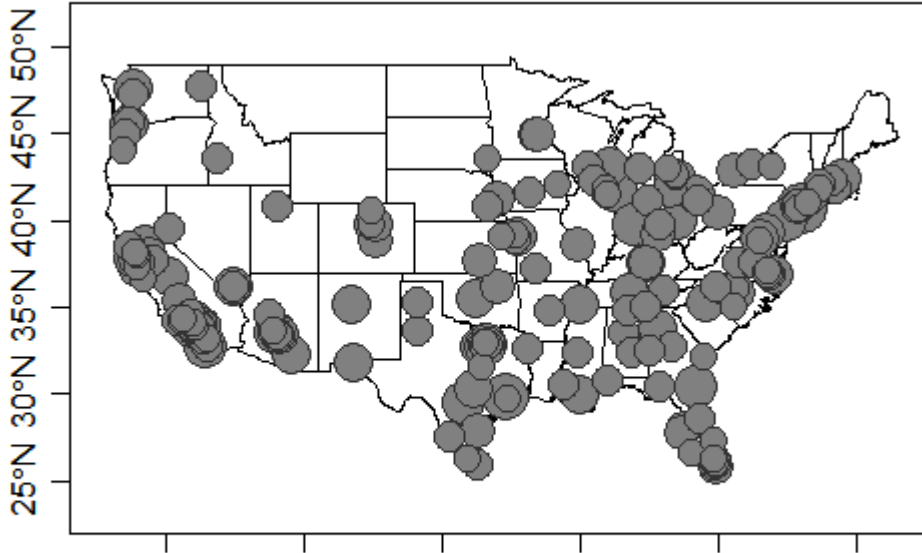


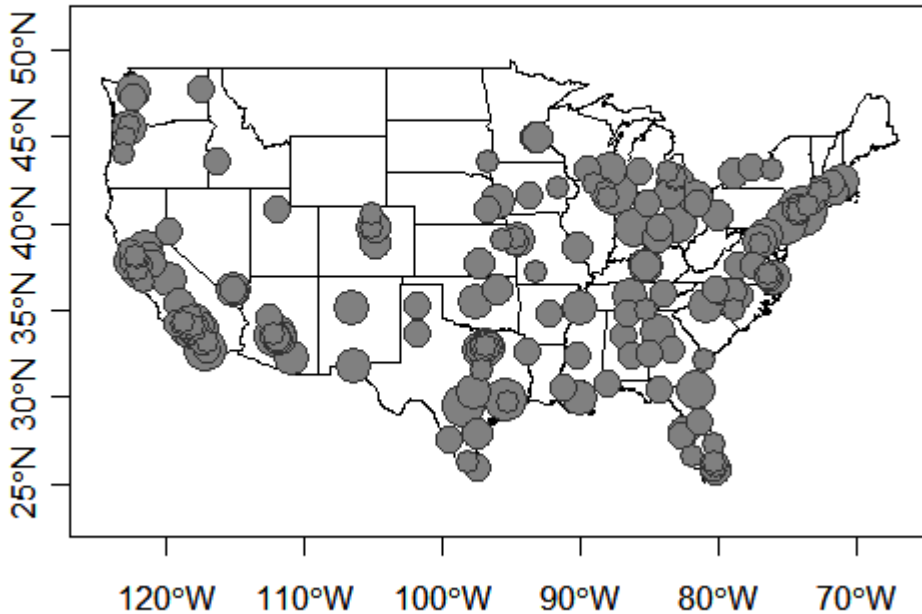
Figure 2 Plot showing the feasible region of the objective function in Figure 1, where the vertical curved plane is the boundary of the constraint $\alpha_1 + \alpha_2 \leq 0.2$.





Probability of detection = 0.5
Expected number of false alarms = 4.55

Probability of detection = 0.6
Expected number of false alarms = 4.55

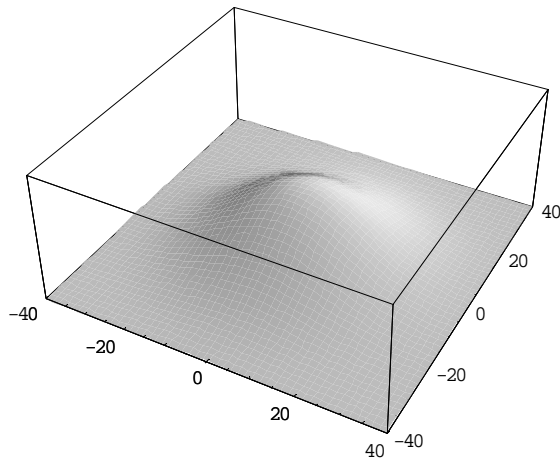


Probability of detection = 0.5
Expected number of false alarms = 4.55

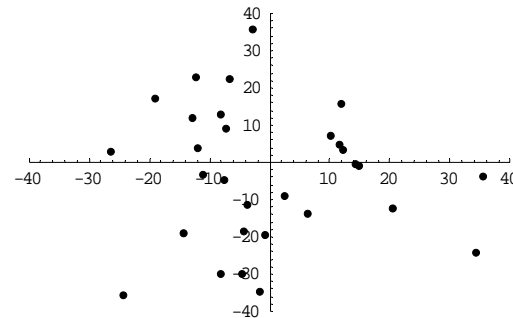
Probability of detection = 0.5
Expected number of false alarms = 2.25

Focus Area #3: Spatio-temporal Methods (Detection and Situational Awareness) [1]

- ER patients come from surrounding area
 - On average, 30 per day
 - More likely from closer distances
 - Outbreak occurs at (20,20)
 - Number of patients increase linearly by day after outbreak



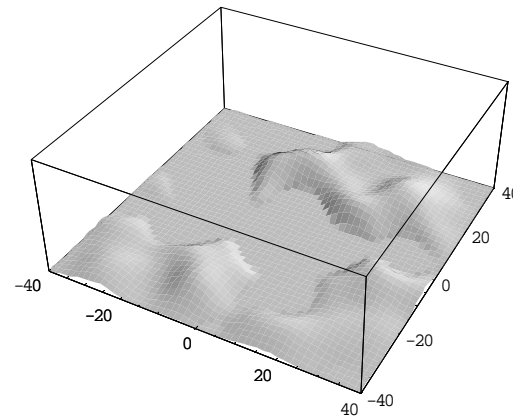
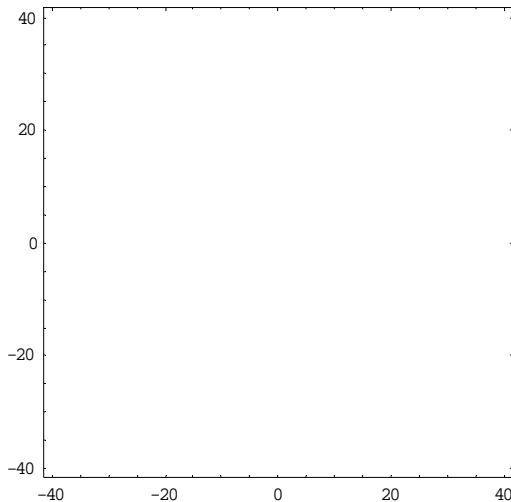
(Unobservable) distribution of ER patients' home addresses



Observed distribution of ER patients' home addresses

Use Difference in Kernel Density Estimates to Assess Outbreak Location

- Construct kernel density estimate of “normal” disease incidence using N historical observations
- Compare to density estimate of most recent w observations



But how to know when to signal?

Idea: Conduct Sequential Hypothesis Test of Distribution of Density Heights

- At each time n , use historical data and recent data to construct density estimate, \hat{f}_n
 - Under no-outbreak condition, density heights of historical and recent observations should be uniformly distributed

- Compute empirical distributions of the two:

$$\hat{J}_n(z) = \frac{1}{w+1} \sum_{i=n-w}^n I\{\hat{f}_n(X_i) \leq z\}, \quad \hat{H}_n(z) = \frac{1}{N} \sum_{i=n-w-N+1}^{n-w-1} I\{\hat{f}_n(X_i) \leq z\}$$

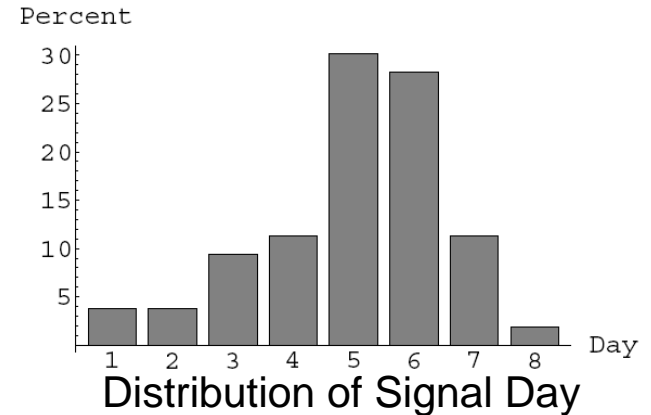
- Use Kolmogorov-Smirnov test to assess when differences are significant:

$$S_n = \max_z \left| \hat{J}_n(z) - \hat{H}_n(z) \right|$$

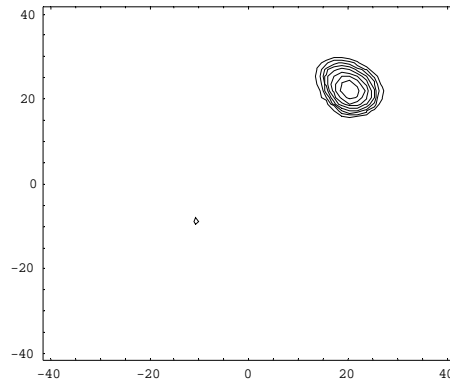
- Signal at time $t = \min \{n : S_n > h\}$

Illustrative Results

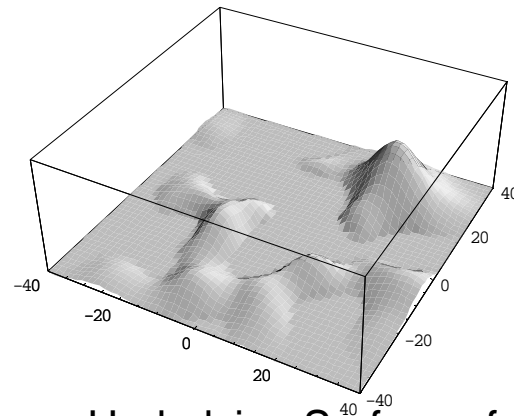
- Assess performance by simulating outbreak multiple times, record when RTR signals
 - Signaled middle of day 5 on average
 - By end of 5th day, 15 outbreak and 150 non-outbreak observations



- From previous example:



Estimate of Outbreak Location on Day 5



Underlying Surface of Density Height Differences

In Summary: Lots of Interesting Research Opportunities

- Control chart experts have a lot to offer
 - Public health community re-inventing SPC?
 - Guidance for how to compare methods
 - Determining metrics for biosurveillance methods
- Syndromic surveillance offers challenges
 - Adapting/extending existing methods
 - Developing and assessing new
 - Univariate and multivariate temporal methods
 - Spatio-temporal methods
 - Strategies for optimizing biosurveillance systems

Selected References

Background Information:

- Woodall, W.H., The Use of Control Charts in Health-Care and Public-Health Surveillance, *Journal of Quality Technology*, **38**, pp. 1-16, 2006.
- Fricker, R.D., Jr., Syndromic Surveillance, *Encyclopedia of Quantitative Risk Assessment* (to appear).
- Fricker, R.D., Jr., and H. Rolka, Protecting Against Biological Terrorism: Statistical Issues in Electronic Biosurveillance, *Chance*, **91**, pp. 4-13, 2006
- Shmueli, G., Statistical Challenges in Modern Biosurveillance, in submission to *Technometrics*.

Selected Research:

- Fricker, R.D., Jr., Hegler, B.L., and D.A Dunfee, Assessing the Performance of the Early Aberration Reporting System (EARS) Syndromic Surveillance Algorithms, in submission to *Statistics in Medicine*.
- Fricker, R.D., Jr., and D. Banschbach, Optimizing a System of Threshold Detection Sensors, in draft.
- Fricker, R.D., Jr., and J.T. Chang, A Spatio-temporal Method for Real-time Biosurveillance, in submission to *Quality Engineering*, 2007.
- Fricker, R.D., Jr., Knitt, M.C., and C.X. Hu, Comparing Directionally Sensitive MCUSUM and MEWMA Procedures with Application to Biosurveillance, in submission to *Quality Engineering*.
- Jones, M.D., Jr., Woodall, W.H., Reynolds, M.R., Jr., and R.D. Fricker, Jr., A One-Sided MEWMA Chart for Health Surveillance, in submission to *Quality and Reliability Engineering International*.
- Fricker, R.D., Jr., Directionally Sensitive Multivariate Statistical Process Control Methods with Application to Syndromic Surveillance, *Advances in Disease Surveillance*, **3**:1.